FEATURED EDITORIAL

Percutaneous coronary revascularisation: is it ever worth what it costs?

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"How could percutaneous coronary intervention without the risks and morbidities of heart surgery not be of benefit to patients? Hard experience teaches that such attractive "pathophysiological" simplifications are unreliable guides to practice and paradoxically may lead to worse rather than better treatment decisions"

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Thirty years ago, Andreas Gruentzig changed the course of medical history when he reported his initial clinical experience with percutaneous coronary intervention (PCI) using balloon catheters. Currently, cardiologists in the UK perform over 70 000 PCI procedures a year, which represents about a 400% increase in volume over the past decade.[1] Similar increases can be found in many European countries and in the USA.[2] Although US doctors perform about 10 times as many procedures as their UK counterparts on a population five times as large, both groups behave as if an ever increasing number of patients with coronary artery disease (CAD) are best served by undergoing PCI. From these observations, and given the growing financial investment implied by the trends, one might conclude that a broad consensus exists about the clinical role of PCI.

The evidence base, however, does not provide the strong support implied by these international practice trends. For example, a recent meta-analysis comparing PCI with conservative medical treatment in 2950 patients from 11 clinical trials found no benefit of intervention on hard cardiac event rates, including death or myocardial infarction (MI).[3] Further, none of the many trials comparing bare metal stents with balloon-only PCI, and more recently, drug-eluting stents with bare metal stents, provides reason to believe that these technological improvements in the PCI procedure have delivered measurable improvements in hard cardiac event rates.[4 5] Only restenosis rates (which reflect procedure-induced complications rather than disease-related complications) have clearly been reduced with the newer technology.

The apparent discrepancy between clinical practice patterns and the available evidence base for PCI may relate to different perceptions of the benefit–risk trade-offs as well as the value provided for money invested. A cost-effectiveness analysis can be helpful in such situations because it requires an explicit specification of all the incremental benefits and all the incremental resources/costs associated with the procedure or treatment in question over the long run (the period during which treatment-related outcomes and costs are likely to accrue).

COST EFFECTIVENESS OF PCI FOR STABLE ANGINA

The major determinants of the cost effectiveness of PCI can be best understood by examining two concepts: the ratio structure of the cost-effectiveness calculation, and the relationship between patient baseline risk and procedure benefit. On the first point, because PCI is almost always more costly than medical treatment alone (both in the short and the long term), in order for the procedure to be associated with a favourably low or "economically attractive" cost-effectiveness ratio, it must produce important increments in life expectancy, quality of life, or both. As can be appreciated from the general formula for calculating cost effectiveness,

$$CE = \frac{C_{New} - C_{Usual\ Care}}{HB_{New} - HB_{Usual\ Care}}$$

where CE = cost effectiveness, C = costs, and HB = health benefits, modest changes in the denominator (incremental health benefits) can have a greater effect on whether the ratio exceeds conventional benchmarks than large changes in the numerator (incremental costs).[6] The benchmark value most often used to decide whether a particular cost-effectiveness ratio is small enough to be judged "economically attractive" is around £30 000 ($61 000) per quality-adjusted life year (QALY) for the UK and $50 000 per QALY for the USA.

In the calculation of the benefits of treatment for a cost-effectiveness analysis, absolute rather than relative effects are what matter. Clearly, a treatment that produces a 20% reduction in mortality when applied to a high-risk population will generate many more survivors per 100 patients treated than when applied to a low-risk population. From these considerations, one can infer that an expensive treatment such as PCI applied to a relatively low-risk population, such as patients with stable angina, might have difficulty demonstrating a large enough absolute effect on survival and other prognostically relevant events to meet benchmark criteria for cost effectiveness.[3]

Abbreviations: ACS, acute coronary syndrome(s); CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention, QALY, quality-adjusted life year

Improvement of quality of life through relief of angina is another potential path by which PCI can demonstrate value for money. In the COURAGE trial, a significant reduction in angina was indeed seen early in the PCI arm.[7] At the 1-year follow-up, eight more patients per 100 treated with PCI were free from angina. However, by 5 years, the two treatment arms had indistinguishable rates of angina. In a cohort study of 1518 non-acute patients with CAD undergoing PCI, Spertus and colleagues showed that the improvement in quality of life after PCI was dependent on the baseline frequency of angina, with clinically significant improvements seen in patients with angina at least once a week.[8] In this cohort, about 60% of patients undergoing PCI had either no angina or had an anginal frequency of less than once a week. Taken together, these data suggest that relief of angina may add less than 10% of the QALY value of saving one extra life, particularly if the results are not durable over the long term.[9]

If the evidence for incremental effectiveness is limited to changes in intermediate end points only, such as increases in coronary patency rates or decreases in objective measures of ischaemia, credible estimation of the effect of treatment on quality-adjusted survival is not possible, since intermediate end points are consistently unreliable markers for patient outcomes.[10]

Effectiveness summaries, such as are provided in meta-analyses or even the reports of major clinical trials such as COURAGE, may obscure important pockets of treatment-related outcome improvement because benefits from a medical treatment are not distributed uniformly in a patient population. In an attempt to explore this issue, Griffin and colleagues applied expert panel ratings of procedural appropriateness (modelled after the RAND methods) to identify patients with CAD most likely to benefit from PCI and from coronary artery bypass grafting.[11] Using a combination of empirical long-term outcomes from a cohort of 1720 patients with CAD together with model-based incremental cost-effectiveness estimates, they found that even in the subgroup judged most appropriate for PCI, the estimated incremental benefits were insufficient to produce an economically attractive cost-effectiveness ratio relative to medical treatment (incremental cost about £2800, cost-effectiveness ratio £47 000 per QALY).

PRIMARY PCI FOR ACUTE ST ELEVATION MI

One area where the use of PCI has found growing acceptance is for reperfusion of patients with acute ST elevation MI.[12 13] Pooled clinical trial analyses have suggested a statistically significant 1–4% or more absolute survival advantage for primary PCI over thrombolytic treatment at 30 days. In this issue of *Heart*, Vergel and colleagues present a model-based, cost-effectiveness analysis of primary PCI versus intravenous thrombolysis for acute ST elevation MI (***see article on page 1238***).[14] Using the available pooled clinical trial data along with data from the Nottingham Heart Attack Registry to estimate long-term outcomes and costs, the authors calculated that primary PCI had a lifetime incremental cost over thrombolysis of about £2700 and added 0.29 QALYs per patient (about 3.5 months of survival in excellent health). From these data the authors concluded that primary PCI had a 90% probability of having a cost-effectiveness ratio of £20 000 or less per QALY. Results were modestly sensitive to variations in the ''door-to-balloon'' time.

Does the demonstration that PCI provides good value for money in the early hours of acute ST elevation MI constitute a proof of concept for cost effectiveness of PCI that can be generalised to other types of patients with CAD? The results of the Occluded Artery Trial (OAT) would suggest not. OAT demonstrated that PCI of occluded infarct arteries in high-risk but stable patients 3–28 days after their acute event provided no improvement in prognosis and only a modest and temporary reduction in subsequent angina.[15]

ACUTE CORONARY SYNDROME: HOW STRONG IS THE EVIDENCE FOR PCI?

Non-ST elevation acute coronary syndromes (ACS) represent another form of higher risk CAD that is commonly treated with PCI. The main ACS treatment strategies involving PCI are structured as ''early invasive'' and ''early conservative'' rather than PCI versus medical treatment. In the early invasive strategy, almost all patients undergo an early coronary angiography and eligible patients then have revascularisation, either PCI or coronary artery bypass grafting, based on the details of their coronary anatomy. In the early conservative strategy, from $<10\%$ to $>50\%$ of patients identified as high risk by various criteria are referred for early angiography, while the remainder is treated medically.

A recent meta-analysis of 8375 non-ST elevation patients with ACS from seven clinical trials reported that all-cause mortality was reduced by 1.6 per hundred treated with the early invasive strategy.[16] This apparently felicitous result, however, obscures some important differences among the trials in the relationship between the prognostic benefits of the early invasive arms and the amount of revascularisation provided by the early conservative arms. In FRISC II, mortality benefits (1.7 extra survivors per 100 patients treated) were demonstrable with the early invasive strategy by minimising use of revascularisation in the early conservative strategy (9% revascularisation within the first 10 days).[17] The early invasive strategy also reduced MIs (2.0 per 100) and provided earlier and better symptom relief. In the RITA 3 trial, which had a 16% hospital angiography rate and a 10% revascularisation rate in the early conservative arm, the death or MI event rate of early invasive management was not different from early conservative treatment at 1 year.[18] However, at 5 years the early invasive strategy was associated with a significantly lower rate of death or MI and a statistically borderline 3 per 100 reduction ($p = 0.054$) in the rate of death alone.[19]

At the other end of the spectrum, with over 50% of the early conservative patients referred for early angiography in the TACTIS-TIMI 18 trial, early invasive treatment had no significant effect on survival but did reduce non-fatal MIs by 2.0 per 100 patients treated.[20] The more liberal use of angiography and revascularisation in the conservative arm narrowed the cost difference between the two strategies to around £330.[21] At 6 months, the early conservative strategy in this trial was less expensive and had a slightly higher quality-adjusted survival than the early invasive arm. Modelling the potential life expectancy benefits from the MIs prevented in the early invasive arm yielded a lifetime cost-effectiveness ratio of about £7200 per life year gained. The results stand in contrast with those of the ICTUS trial, which employed a similar early conservative strategy (53% with angiography during the initial hospitalisation) but failed to demonstrate any prognostic advantage for early invasive treatment.[22] Despite the requirement for all enrolled patients to have a positive troponin test at entry, the event rates in the early conservative strategy arm up to 1 year in ICTUS were lower than those in the comparable TACTICS-TIMI 18 patients, which may explain the apparent discrepancy between these two studies.

IMPLICATIONS FOR CLINICAL PRACTICE AND HEALTH POLICY

In the law, there is a well-established principle known as *res ipsa loquitor* or ''the thing speaks for itself.'' For interventional cardiologists, PCI appears to provide a medical example of this principle. How, they ask themselves, could the restoration of demonstrably normal antegrade coronary blood flow in major epicardial coronary arteries without the risks and morbidities of heart surgery not be of benefit to patients, since coronary

obstructive disease is clearly an adverse prognostic factor? Hard experience has taught that such attractive ''pathophysiological'' simplifications are unreliable guides to practice and at times may lead to paradoxically worse rather than better treatment decisions.[23]

On the other hand, a superficial reading of the clinical trial evidence and the economic analyses based on these data may also provide misdirection of care and policy. The trials in stable angina, for example, do not test pure strategies of ''PCI'' versus ''medicine'' but rather routine PCI versus selective, and in some cases, deferred, PCI added to best medical care. The COURAGE results might well have appeared more favourable for intervention if investigators had not permitted over 30% of the medical arm subjects to cross over. The fact that we would be uncomfortable with such a draconian trial design implies an underlying consensus that PCI does provide clinically important benefits under at least some circumstances.

Because clinical trials are too unwieldy to test the multiple permutations of invasive and conservative strategies that can occur in practice, we must be more willing to employ carefully crafted statistical and decision models to meld the general proofs of clinical trials with the detailed clinical risk and outcome data provided by high-quality observational databases. The result, one hopes, will be a more nuanced, economically efficient, patient-centred matching of disease-related risks and expected treatment-related benefits.

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